ASCPT Annual Meeting
Clinical Pharmacology Curriculum Review Course
Orlando, FL
March 6, 2005

Clinical Trials and Drug interactions

Shiew-Mei Huang, Ph.D.
Deputy Office Director for Science
Office of Clinical Pharmacology & Biopharmaceutics
CDER, FDA

Recent US Market Withdrawal (1998-2003) **

Withdrawn	Approval	Drug name	Use	Risk
1998	1997	Mibefradil	High blood pressure/ Chronic stable angina	Drug-drug interactions Torsades de Pointes
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1988	Astemizole	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de Pointes
2000	2000	Alosetron*	Irritable bowel syndrome in women	Ischemic colitis; complications of constipation
2000	1993	Cisapride	Heartburn	Torsades de Pointes Drug-drug interactions
2000	1997	Troglitazone	Diabetes	Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis Drug-drug interactions
2001	1999	Rapacuronium	Anesthesia	Bronchospasm

*Reintroduced in 2001; ** rofecoxib (Vioxx) withdrawn in Sept 2004; natalizumab (Tysabri) withdrawn in Feb 2005

<Table from Huang SM, Miller M, Toigo T, Chen MC, Sahajwala C, Lesko LJ, Temple R, Evaluation of Drugs in Women: Regulatory Perspective– in Section 11, Drug Metabolism/Clinical Pharmacology (section editor: Schwartz, J), in “Principles of Gender-Specific Medicine”, Ed., Legato M, Academic Press (2004) >

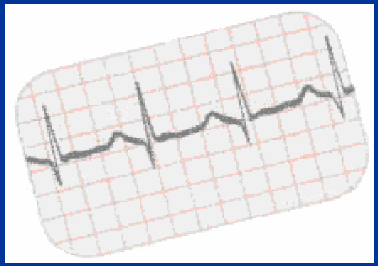
What do they have in common?

1. Terfenadine (1985-1998)
2. Mibefradil (1997-1998)
3. Astemizole (1988 - 1999)
4. Cisapride (1993-2000)
5. Cerivastatin (1997-2001)

Drug-drug interactions

Unacceptable risk/benefit ratio

- QTc prolongation



- Rhabdomyolysis

CYP3A4

3: substrate

1: inhibitor

CYP2C8

UGT

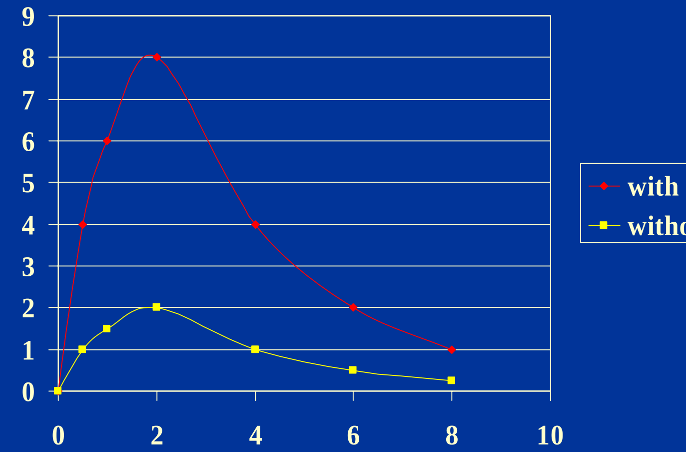
others

Inhibitor

Mibefradil

Terfenadine
Astemizole
Cisapride

CYP3A → X Metabolites

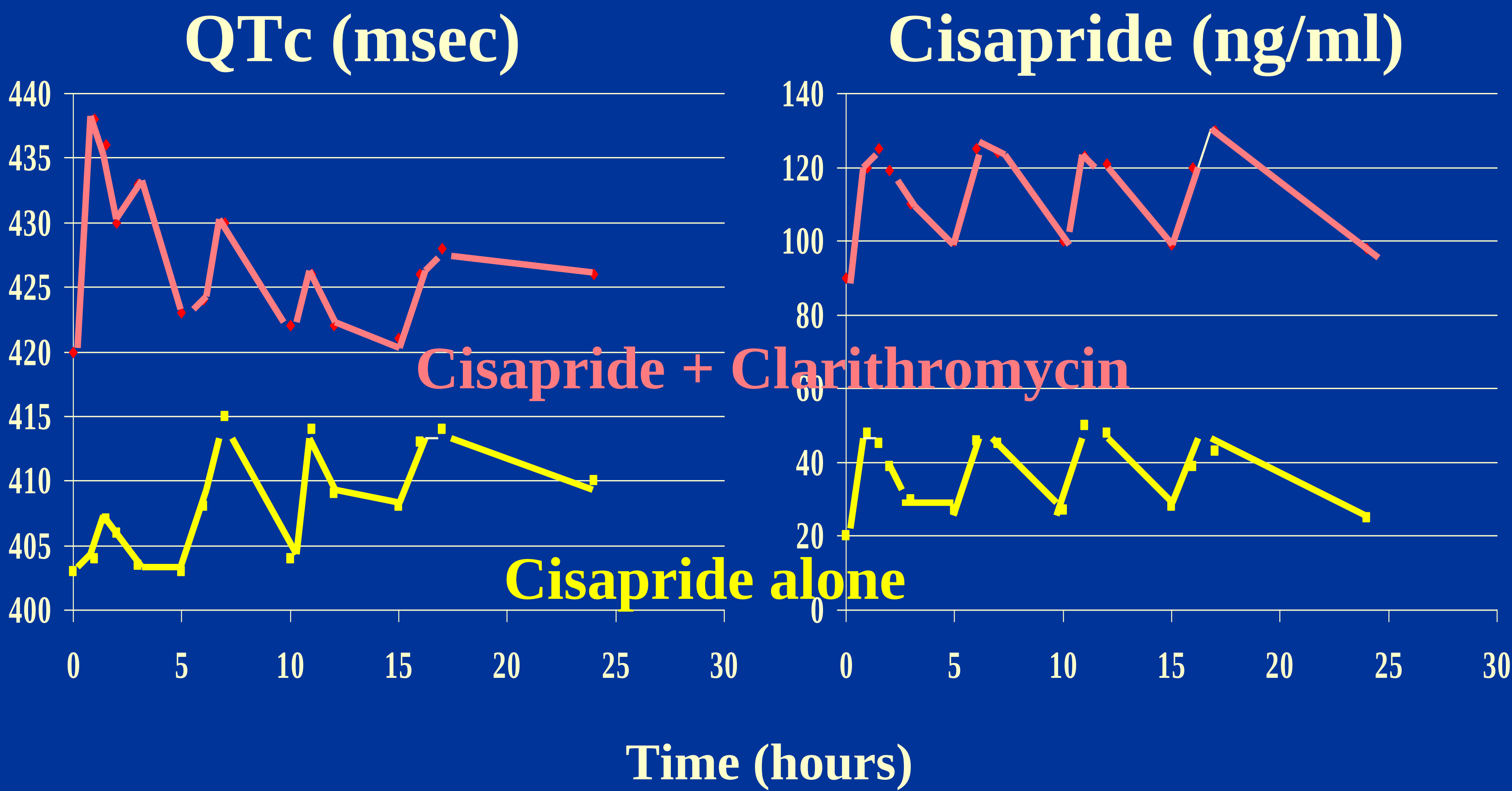


CYP2C8
UGT
CYP3A
transporters
others

Cerivastatin → Metabolites

- **Need to evaluate other drugs' effects on the new molecular entity (NME) and the NME's effects on other drugs**
- **Experience from recent non-approval: need to evaluate inhibition as well as induction**

Cisapride



< Data taken from van Harrsrt AD, et al, Clin Pharmacol Ther 1998 Nov; 64(5): 542-6 >

Adverse Drug Reactions- Marketed Drugs

- **2,000,000**

  number of serious ADRs yearly

- **100,000**

  annual number of ADR-related deaths

- **4-6**

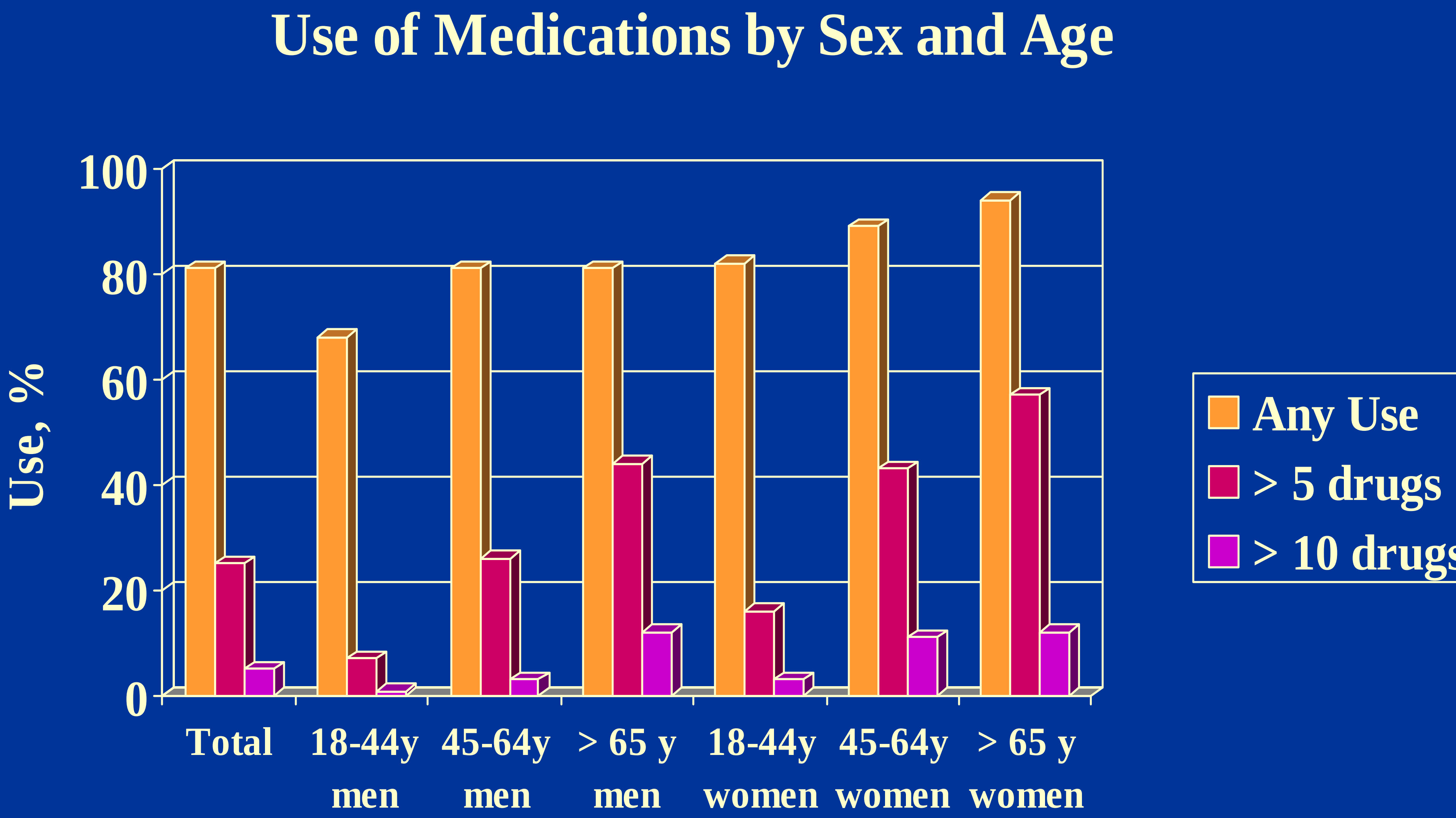
  ranking of serious ADRs as causes of death

- **136,000,000,000**

  annual cost in dollars associated with ADRs

< *JAMA* 1998;279:1200–1205; *Arch Intern Med* 1995;155(18):1949–1956>

Why are there so many ADRs?



< JAMA 2002;287:337-344 >

“…drug interactions represent 3-5% of preventable ADRs and are an important contributor to ER visits and hospital admissions.”

< JAMA 1995;274(1):35–43>

“…elderly patients with digoxin toxicity were 12 times more likely to have been treated with clarithromycin”

< JAMA 2003;289 (13):1652>

What lessons have we learned? Questions to ask when review NDA/ Post-marketing data

1. Drug interaction an issue

Yes ↓

2. Benefit outweigh risk?

No → **Not-approvable**

Yes → **Can we manage through labeling?**

↓

- **Assign levels of risk**
- **Education for healthcare providers & patients**

< Lesko, L, et al, QA/QC Report, 2000; Huang S-M, et al, Clin Pharmacol Ther 2000; 67(2): 148; Huang, S-M, Drug-drug interactions, in « Applications of Pharmacokinetic Principles in Drug Development », Ed. Rajesh Krishina, Kluwer Academic/Plenum Publishers, 2003 >

Clinical Pharmacology and Biopharmaceutics Review

Good Review Practices: Clinical Pharmacology & Biopharmaceutics Review Template: http://www.fda.gov/cder/mapp/4000.4.pdf, April 2004

Extrinsic factors

Environmental **Smoking/Diet**

Medical Practice **<u>Drug-drug interaction</u>**

Intrinsic factors

Gender

Genetics

Race

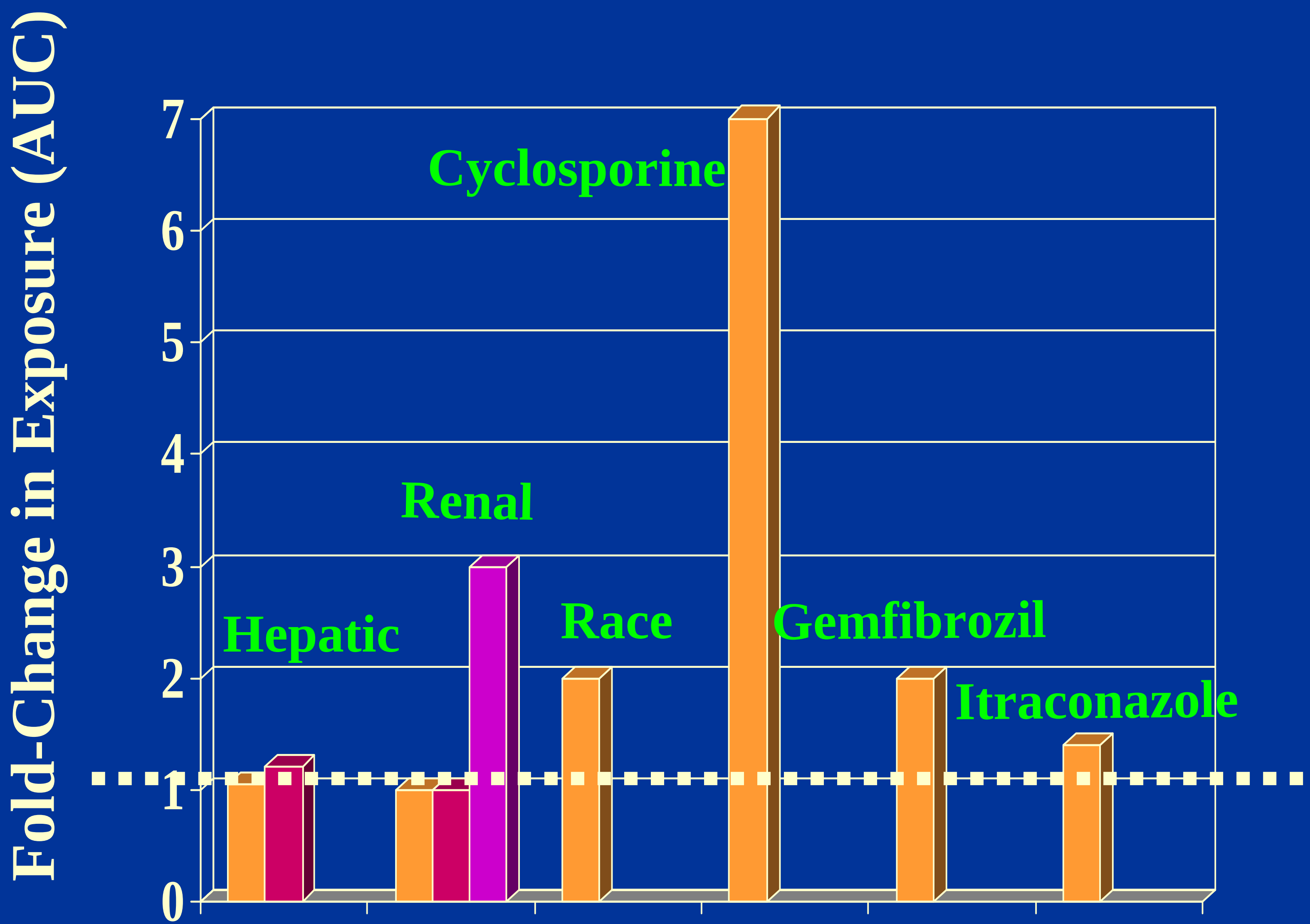
Age ***Organ Dysfunction*** ***Disease***

Pregnancy

Lactation

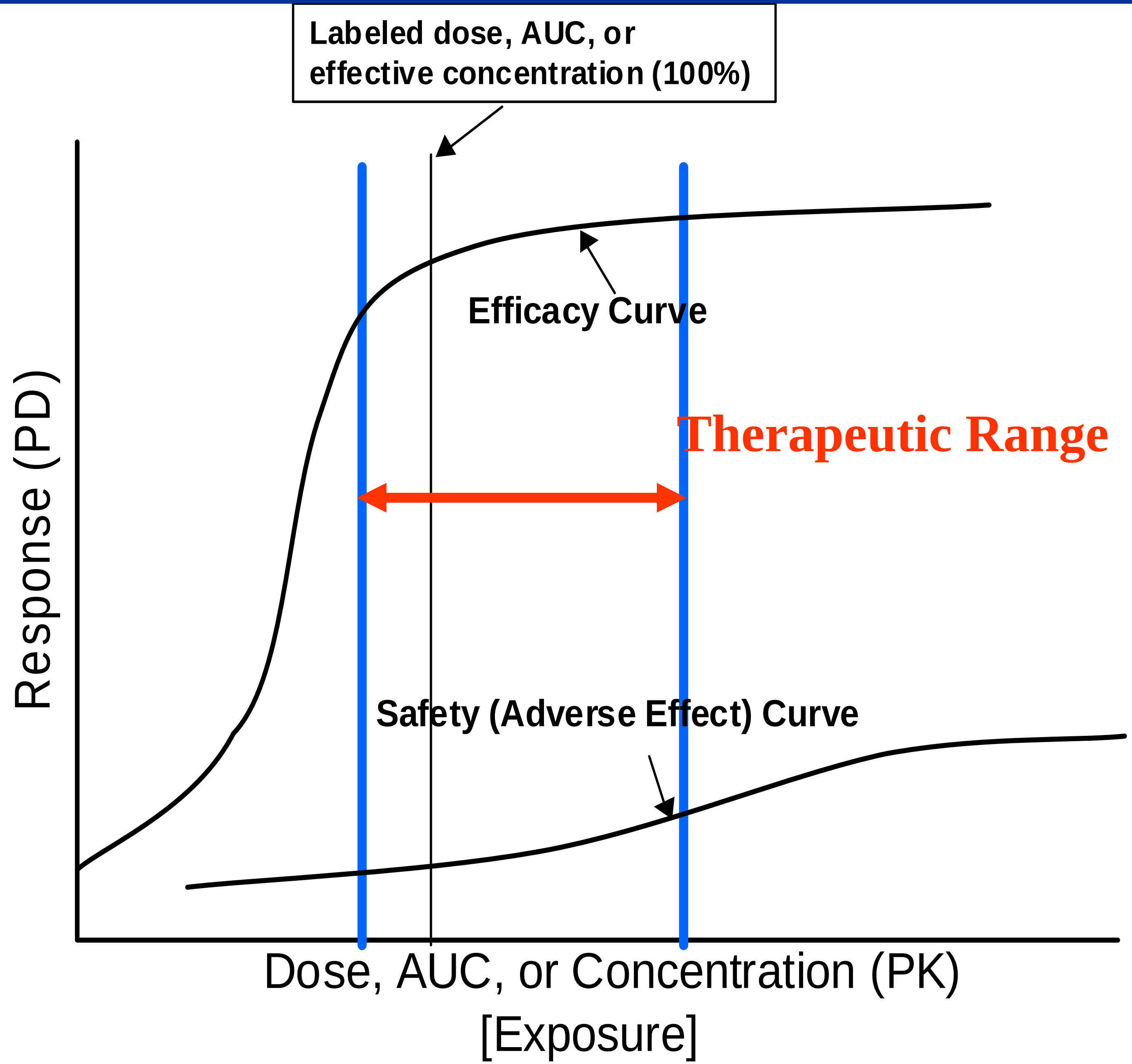
Adapted from ICH E5, 1998: http://www.fda.gov/cder/guidance/2293fnl.pdf

Evaluation of systemic exposure changes in specific populations

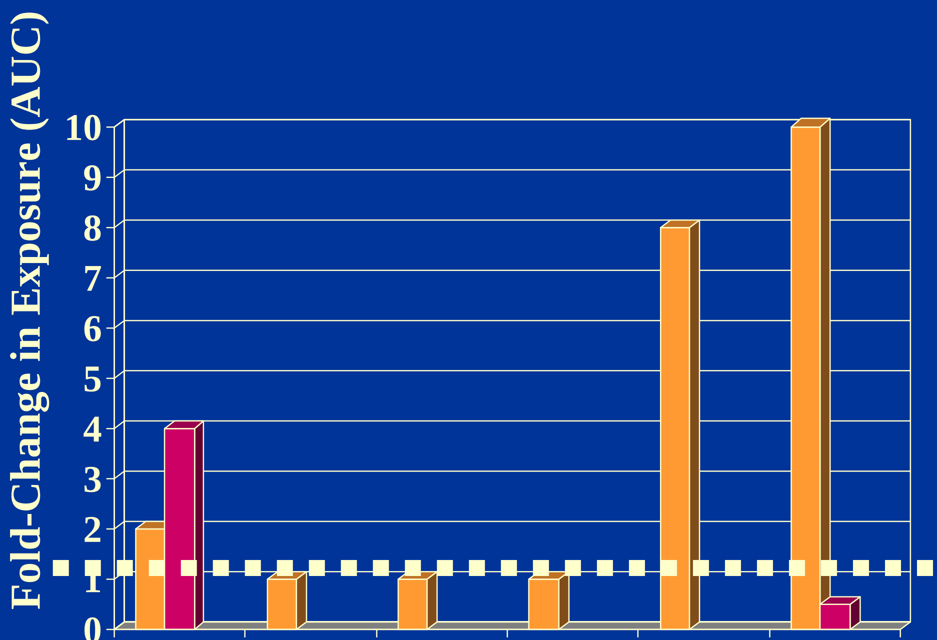


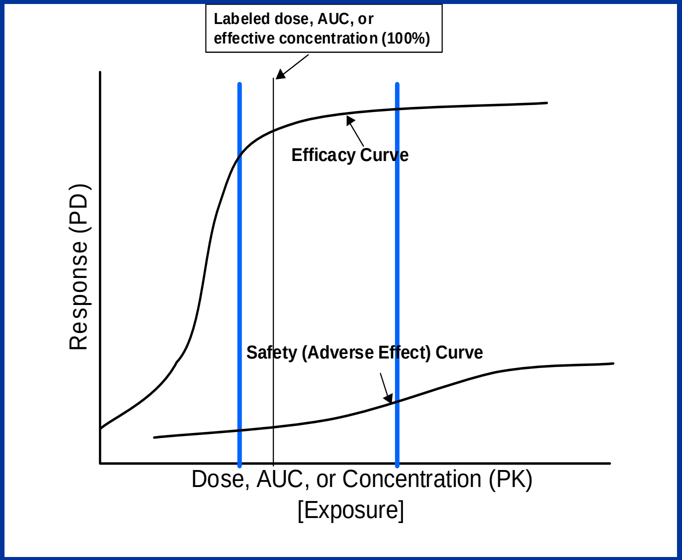
< Data compiled from PDR entry for CRESTOR® (AstraZeneca) (rosuvastatin calcium) labeling>

Establishment of exposure - response relationship



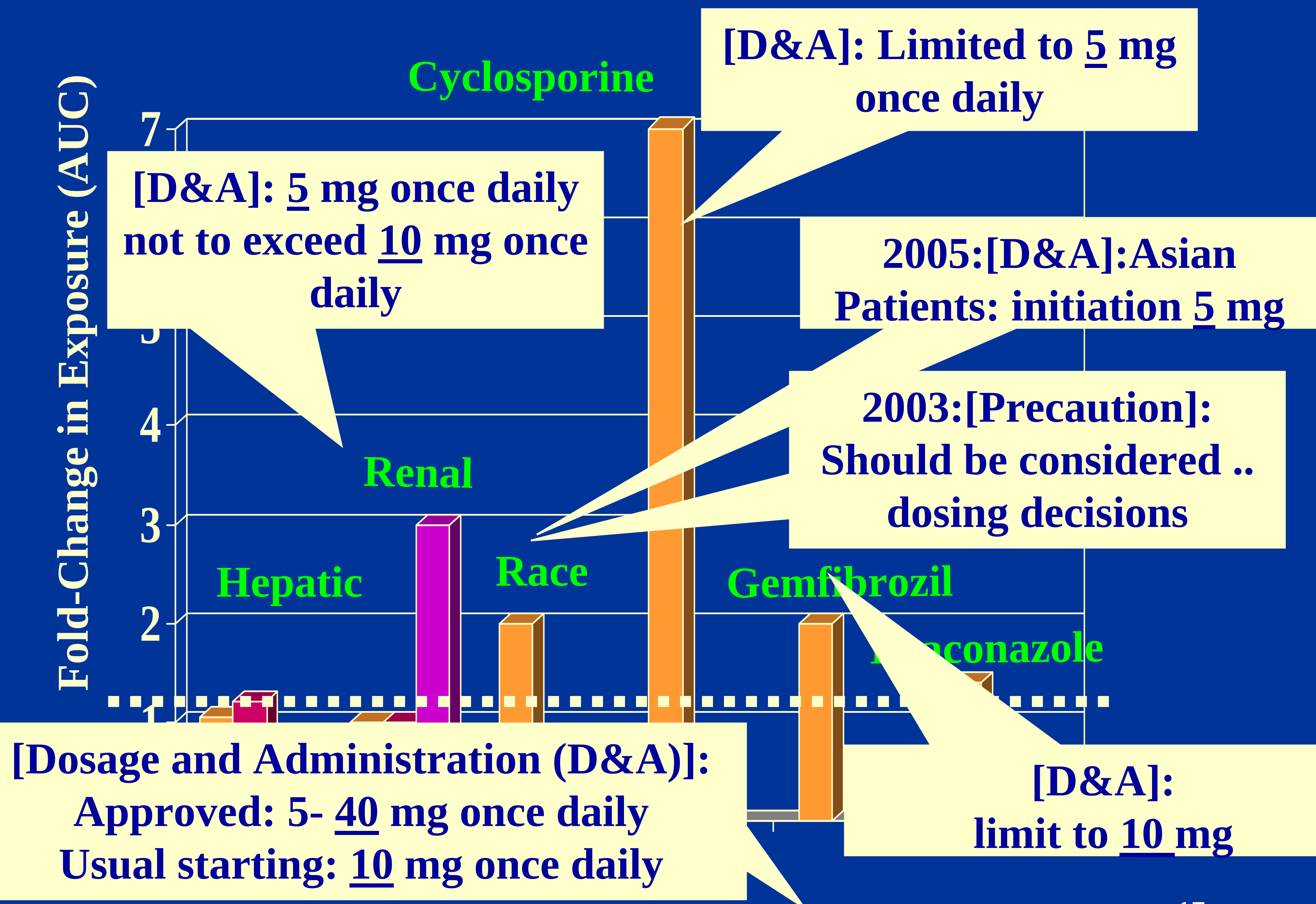
< Huang and Lesko, J Clin Pharmacol, 44: 559. June 2004>





Labeling recommendations

Other considerations



< Data compiled from PDR entry for CRESTOR® (rosuvastatin) labeling>

Evaluation of
Drug Interactions

Concept Paper

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm

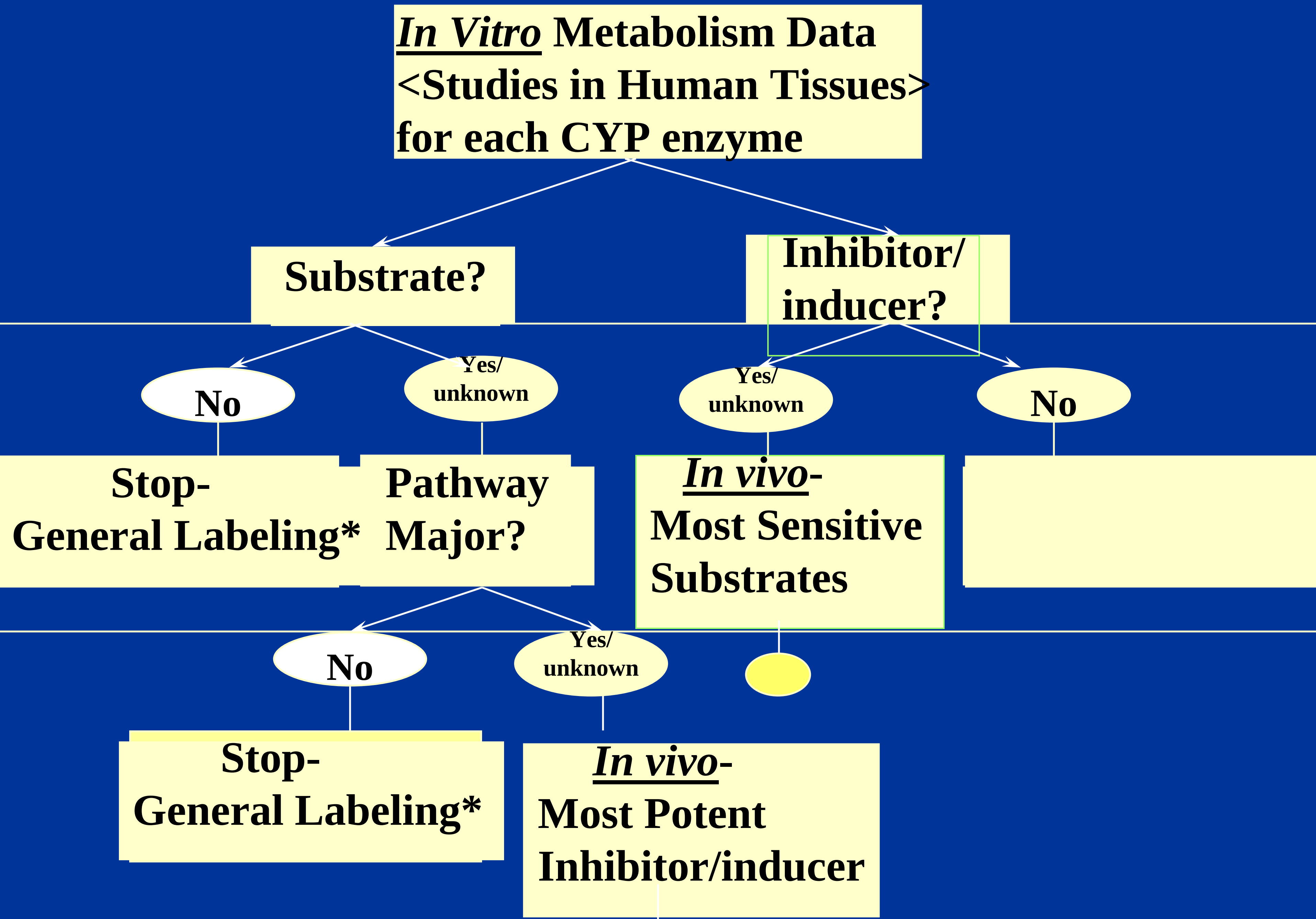
What is optimal drug interaction information from NDA submissions?

- Elucidation of metabolic pathways; contribution of CYP; fraction metabolized

  - Effect ***of*** other drugs

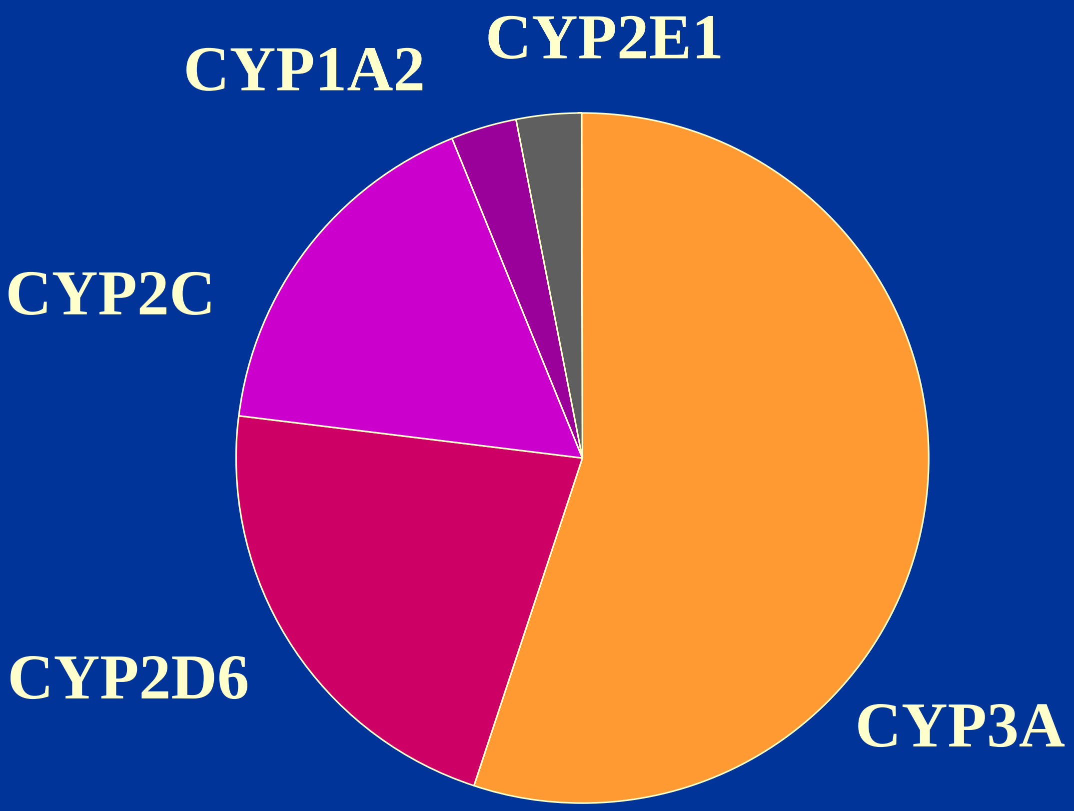
- Enzyme modulating potential (inhibition/induction by NME/metabolites)

  - Effect ***on*** other drugs



*Population PK studies

Proportion of drugs metabolized by the major cytochrome P450 enzymes



< Data taken from Godman & Gilman's The pharmacological basis of therapeutics, 9th ed., 1996>

Evaluation of metabolic interactions

Inhibition CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP2D6

Induction CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A

Metabolic Profiling CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP2D6

Other CYPs/Phase 2 metabolism

Case 1-
Drug as an inhibitor

Evaluation of inhibition (1)

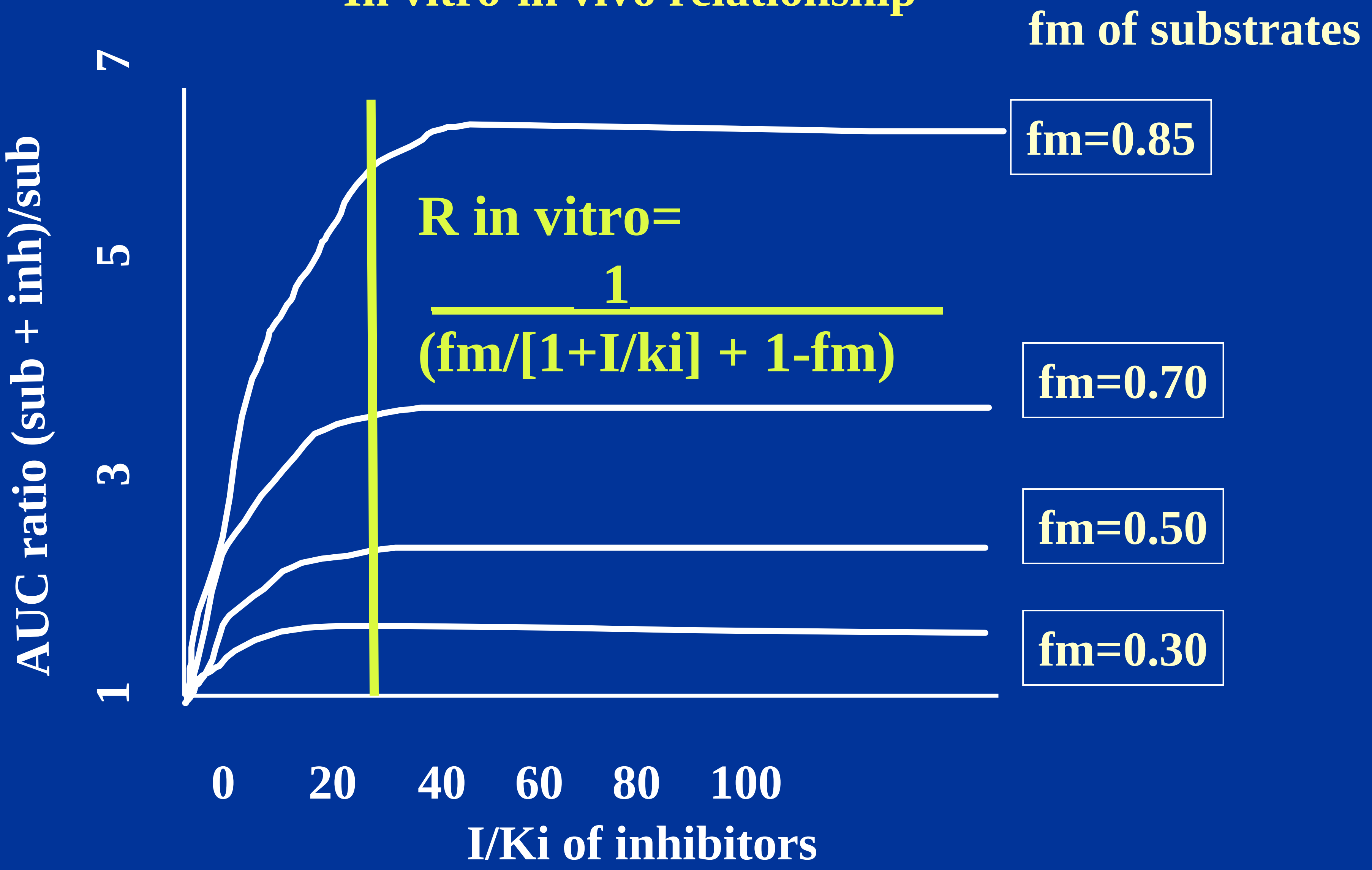
- Competitive inhibition

$$Cl\ ratio = 1/\{[fm/(1+\mathit{I/Ki}] + (1-fm)\}$$

- **Cl : Clearance**
- **Ki : Inhibition constant**
- **I : Concentration of inhibitor at the enzyme site**
- **fm: fraction of substrate dose metabolized by specific enzyme**

Evaluation of inhibition (2)

- In vitro-in vivo relationship



<adapted from Rodrigues, D Wong S, Attempting in vitro-in vivo correlation, in Pharmacogenetics, eds Schlegel, Hori, IBC, 1996>

Evaluation of inhibition (3)

"The likelihood of an in vivo interaction is projected based on the [I]/Ki ratio where [I] represents the mean steady-state Cmax value for total drug (bound plus unbound) following administration of the highest proposed clinical dose. As the ratio increases, the likelihood of an interaction increases."

Prediction of clinical relevance of competitive CYP inhibition

I/Ki	***Prediction***
I/Ki > 1	***Likely***
1> I/Ki> 0.1	***Possible***
0.1> I/Ki	***Remote***

An estimated I/Ki ratio of greater than 0.1 is considered positive and a follow-up in vivo evaluation is recommended.

Evaluation of inhibition (4)

Design the *in vivo* evaluation based on *in vitro* data

- **Initial prediction based on I/Ki**
- **rank order and evaluate the more potent ones, smaller Kis, first)**

NME (Cmax 1uM)

	IC50	Ki	I/Ki
CYP1A2	**50 uM**	**40 uM**	**0.02**
CYP2C8	**>100 uM**	**--**	
CYP2C9	**20 uM**	**10 uM**	**0.1**
CYP2C19	**>100 uM**	**--**	
CYP2D6	**>100 uM**	**--**	
CYP3A4	**7uM**	**2 uM**	**0.5**

Evaluate in vivo first

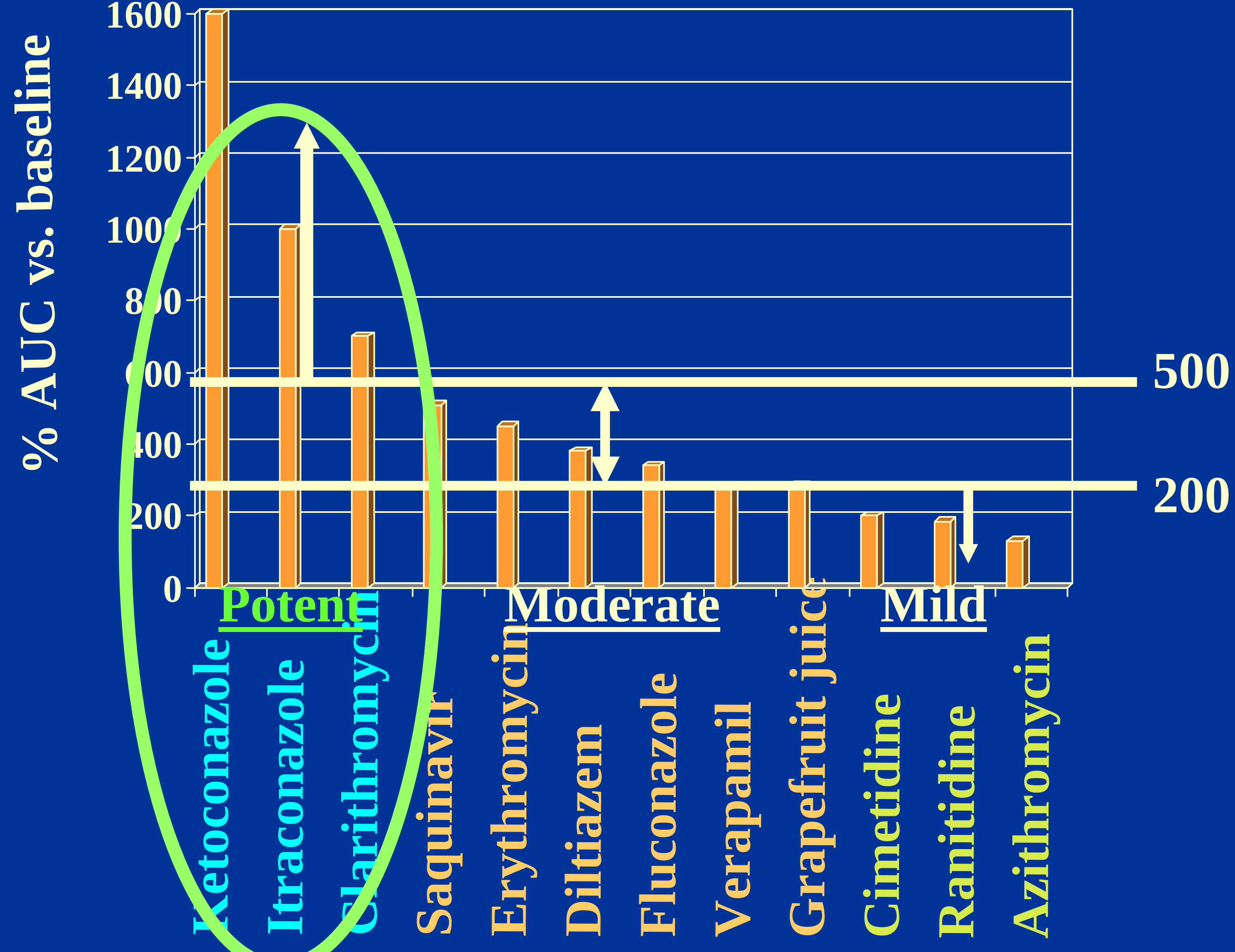
Evaluation of inhibition (5)

- Drug as a CYP3A inhibitor

Drug with	AUC	Cmax
Midazolam	6x	3x
Simvastatin	8x	5x
Cisapride	3x	2x

Evaluation of inhibition (6)

- Drug as a CYP3A inhibitor: midazolam as a probe substrate



< Definition adapted from PhRMA white paper, Bjonrsson, et al, Drug Metab Dispos July 2003 and J Clin Pharmacol, May 2003 >

Evaluation of inhibition (7)
- Labeling

If a drug has been determined to be a strong inhibitor of CYP3A, it does not need to be tested with all CYP3A substrates to warn about an interaction with "sensitive CYP3A substrates" and "CYP3A substrates with narrow therapeutic range".

< adapted from http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htmhttp://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm>

Evaluation of inhibition (8)

- Examples of sensitive CYP3A substrates or CYP3A substrates with NTR

Sensitive CYP3A substrates	CYP3A Substrates with Narrow therapeutic range
budesonide, buspirone, eletriptan, felodipine, imatinab, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil	Alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)

"sensitive CYP3A substrates" refer to drugs whose plasma AUC values are increased 5-fold or more when co-administered with CYP3A inhibitors; "CYP3A substrates with narrow therapeutic range" refer to drugs whose exposure-response data are such that increases in their exposure levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes); (a) not available in US

< adapted from http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htmhttp://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm>

Evaluation of inhibition (9)

- Labeling example- CYP3A inhibitor

<u>Telithromycin</u>	<u>AUC</u>
Midazolam	6x

- Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system
- Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided
- The use of KETEK is contraindicated with cisapride, pimozide

Not studied

<Pysicians' Desk Reference at http://pdrel.thomsonhc.com/pdrel/librarian >

Case 2-
Drug as a substrate

Drug as CYP3A substrate

Drug with	Drug AUC	Drug Cmax
Ketoconazole	8x	4x
Erythromycin	6x	3x
Verapamil	5x	3x

Labeling

If a drug has been determined to be a sensitive CYP3A substrate or a CYP3A substrate with a narrow therapeutic range, it does not need to be tested with all strong or moderate inhibitors of CYP3A to warn about an interaction with "strong" or "moderate" CYP3A inhibitors

< adapted from http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htmhttp://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm>

Examples of strong and moderate CYP3A inhibitors

Strong CYP3A inhibitors	Moderate CYP3A inhibitors
atanazavir clarithromycin indinavir itraconazole ketoconazole nefazodone nelfinavir ritonavir saquinavir telithromycin voriconazole	amprenavir aprepitant diltiazem erythromycin fluconazole fosaprenavir grapefruit juice(a) verapamil

A “strong inhibitor” is one that caused a ≥ 5-fold increase in the plasma AUC values of CYP3A substrates (not limited to midazolam) in clinical evaluations

A “moderate inhibitor” is one that caused a ≥ 2- but < 5-fold increase in the AUC values of sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations

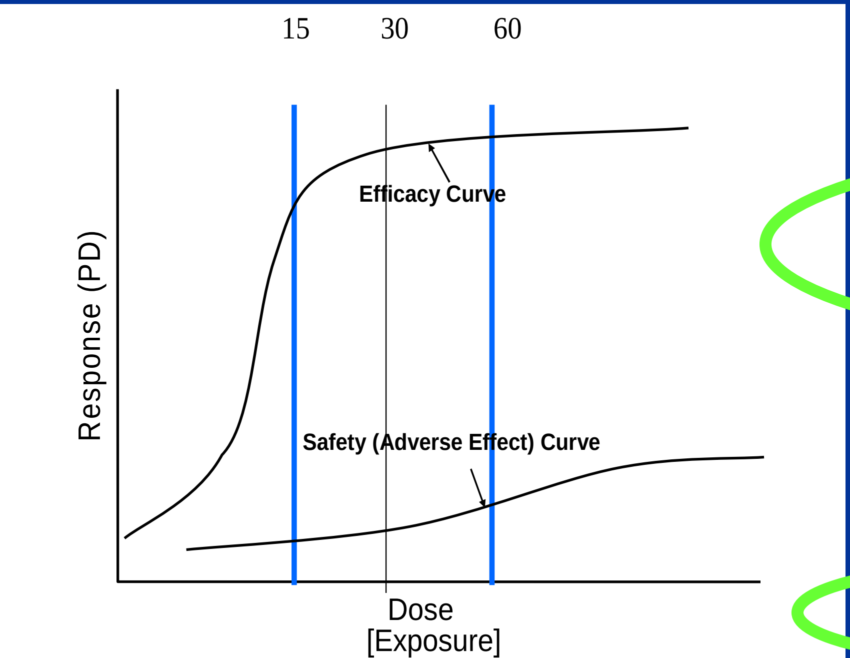
(a) The effect varies widely

< adapted from http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htmhttp://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm>

Labeling example - CYP3A substrate

Drug with	Drug AUC	Drug Cmax
Ketoconazole	8x	4x
Erythromycin	6x	3x
Verapamil	5x	3x

[if approved]



Do not take with strong CYP3A inhibitors….

Ketoconazole,
itraconazole, ritonavir, nelfinavir,
nefazodone, clarithromycin.

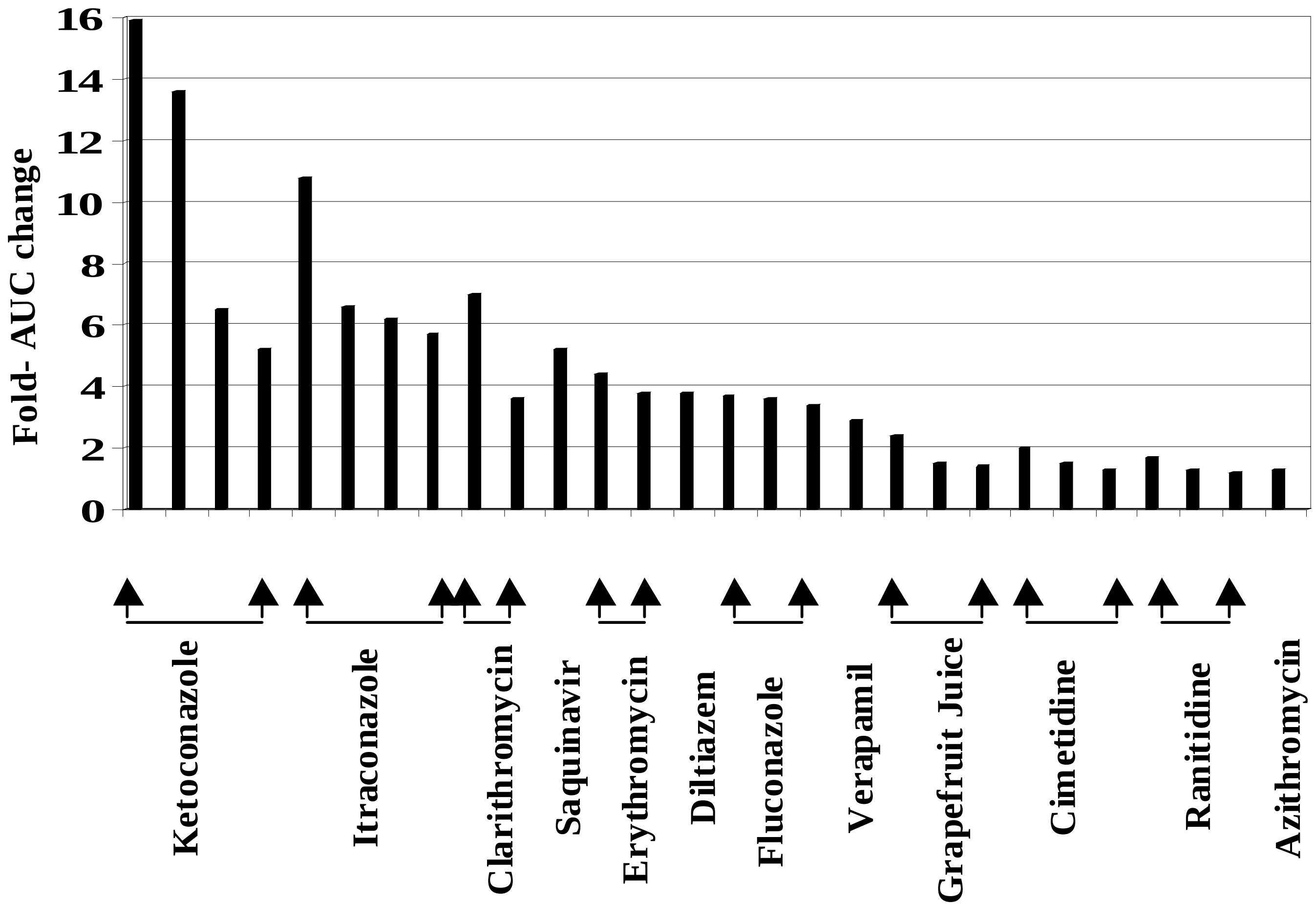
Use lower dose with
moderate CYP3A inhibitors…..

erythromycin, verapamil,
diltiazem...

Not studied

Clinical Study Designs

Figure 2a. Fold-changes of oral midazolam AUC in the presence of various CYP3A inhibitors under varied study conditions (dose, dosage regimen, dosing length, dosing time, etc) for either drug (data obtained from PubMed via *University of Washington Metabolism and Transport Drug Interaction Database* (http://depts.washington.edu/didbase/)- searched up to January 2000)



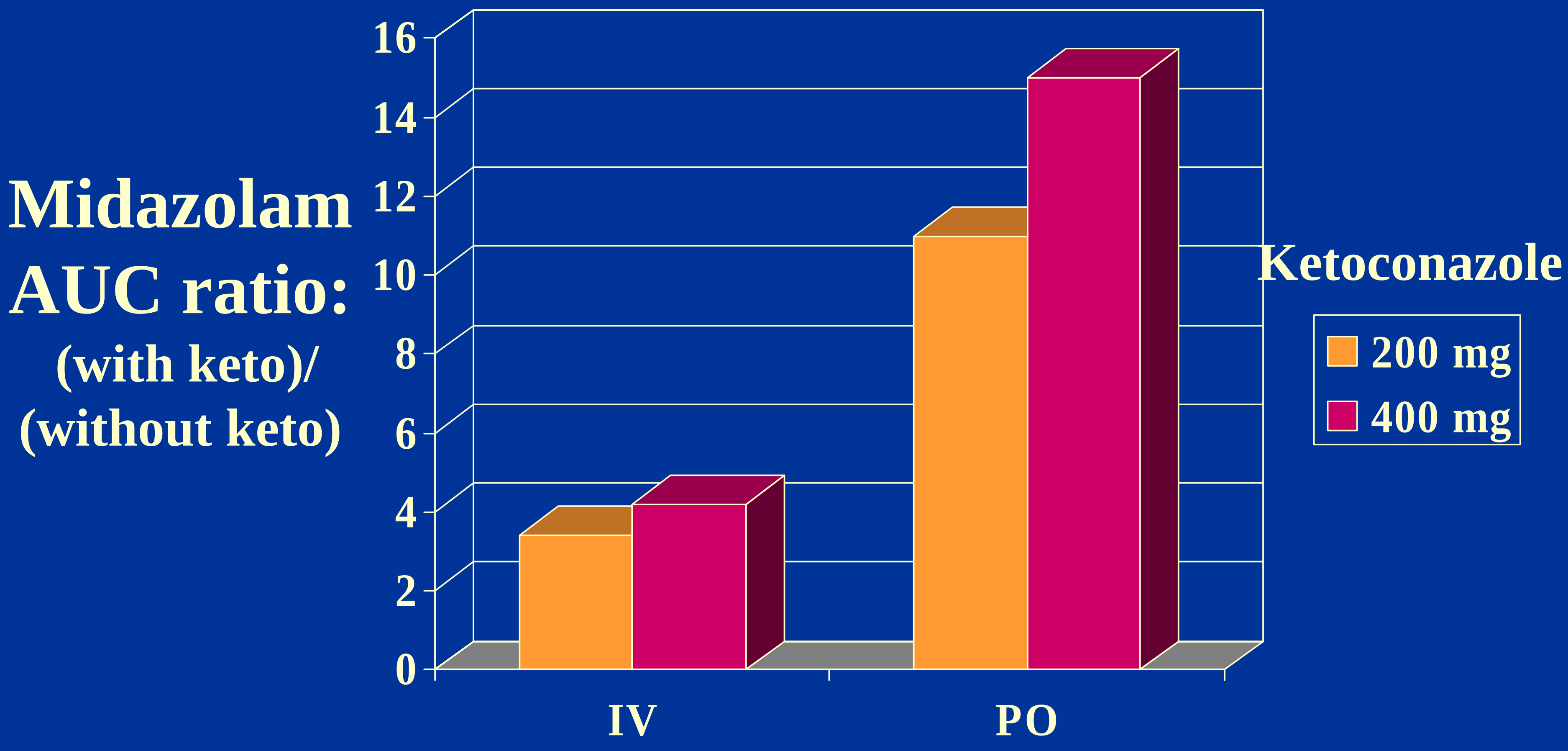
< Huang, S-M, "Drug-Drug Interactions", in « Applications of Pharmacokinetic Principles in Drug Development », Ed. Rajesh Krishina, Kluwer Academic/Plenum Publishers (October, 2003)

Differences in

- **dose**
- **dosing regimens**
- **route of administration**
- **other design issues**

Ketoconazole
(inhibition of CYP3A…..)
200 vs 400 mg

CDER/Indiana University study -within study comparison



<Data from Lucksiri, et al, submitted, ASCPT, 2005; Research Cooperative Agreement: CDER and Indiana University - preliminary data in 15 subjects (IV 0.05 mg.kg, PO 4 mg; 6-7 days of ketoconazole>

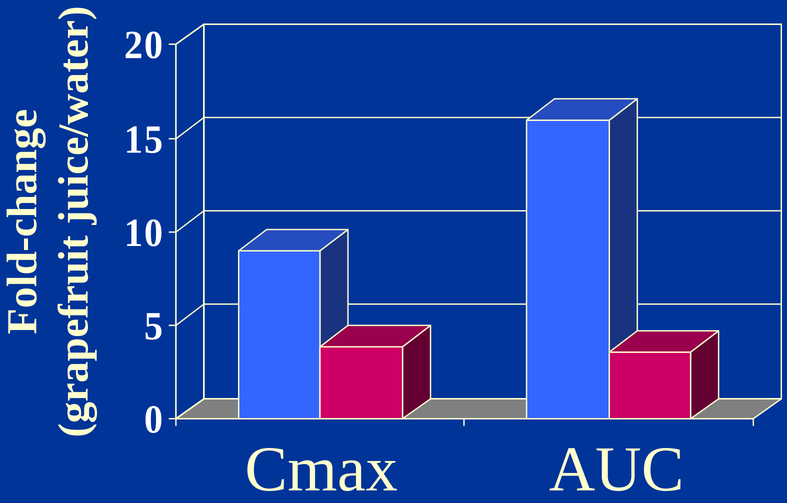
Grapefruit juice
(inhibition of CYP3A…..)

- different preparations
- different dosing regimens

Varied Study Designs/Outcomes

Simvastatin

(similar results with simvastatin acid)



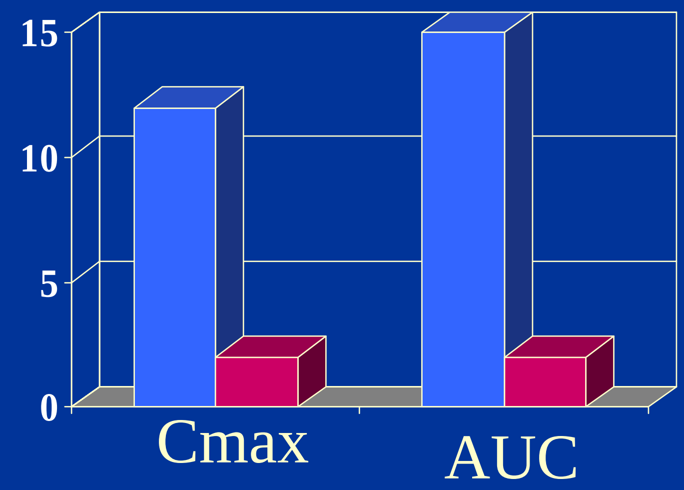
Study 1 200 mL for 3 days
double-strength grapefruit juice
Day 3: (0, 0.5, 1.5 hr)

Study 2 200 mL for 3 days
<u>regular grapefruit juice</u>
<u>Day 3: (*0 hr*)</u>

<Lilja et al, CPT 1998>
< Lilja et al, BJCPT 2004>

Lovastatin

(similar results with lovastatin acid)



Study 1 200 mL for 3 days
double-strength grapefruit juice
Day 3: (0, 0.5, 1.5 hr)

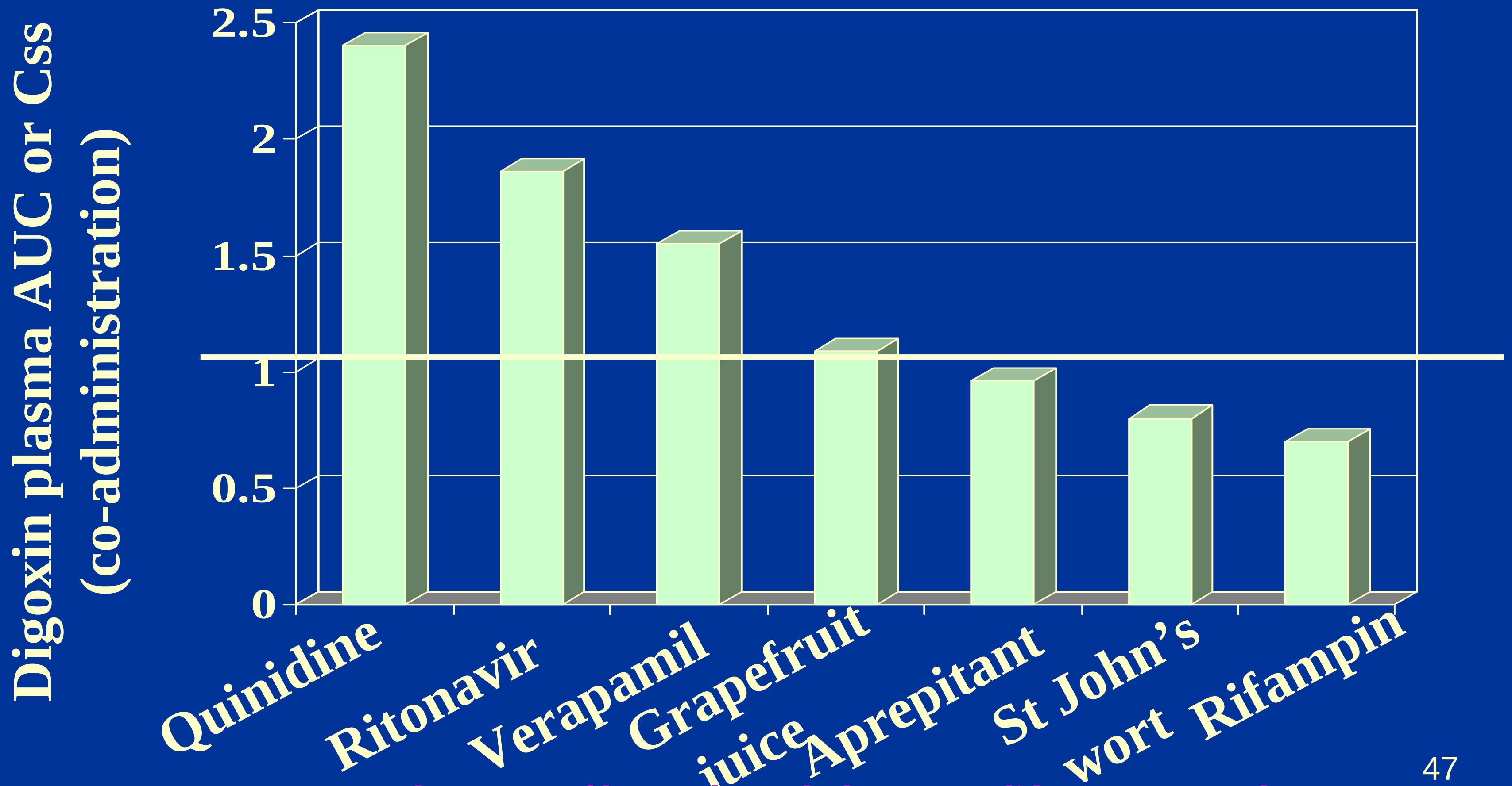
Study 2 200 mL for 3 days
<u>regular grapefruit juice</u>
<u>Day 3: (-12 hr)</u>

<Kantola et al, CPT 1998>
< Rogers et al, CPT 1999>

P-gp and other transporter- based interactions

P-gp transporter based interaction (1)

If a NME is an inhibitor of P-gp in vitro, in vivo study using digoxin may be appropriate



Huang, S-M, ACPS presentation, , http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm

Table. Drug interactions due to inhibition of transport proteins

Substrate	Inhibitor	Transporter
digoxin	quinidine, verapamil, itraconazole	P-gp; OATP
fexofenadine	ketoconazole, erythromycin, azithromycin	P-gp; OATP
talinolol	verapamil	P-gp
loperamide	quinidine	P-gp
dofetilide procainamide levofloxacine	cimetidine	OCT;OAT; OATP
penicillins ACE inhibitors Antiviral drugs	probenecid	OAT
paclitaxel	valspodar	P-gp

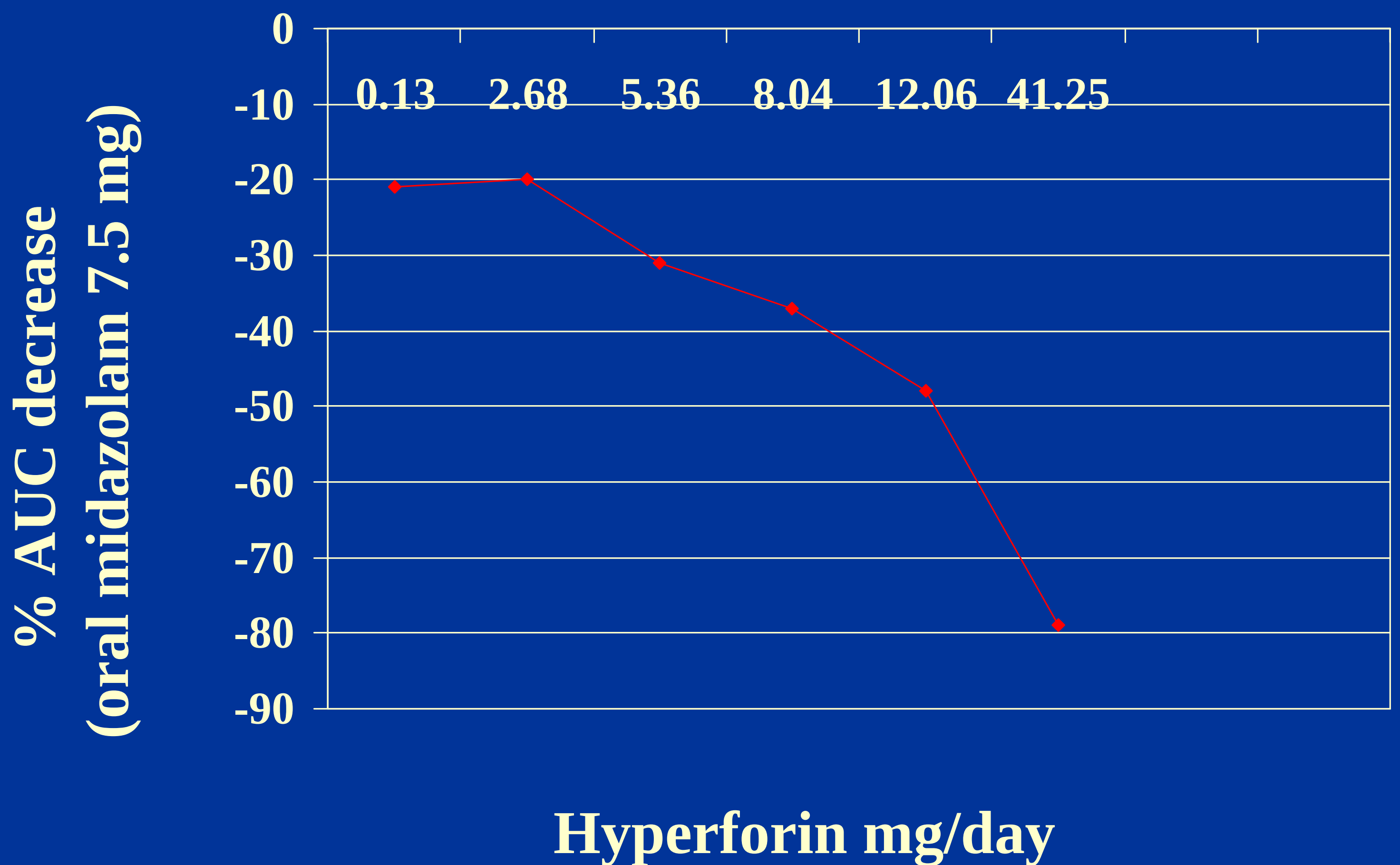
P-gp: p-glycoprotein; OAT: organic anion transporter; OCT: organic cation transporter: OATP: organic anion transport protein

< Adapted from PhRMA white paper, Bjonrsson, et al, Drug Metab Dispos July 2003 and J Clin Pharmacol, May 2003 >

Interactions with dietary supplements

Dr. Gorski's presentation

Hyperorin content



< data taken from Mueller SC, et al, Clin Pharmacol Ther, Febryary, 2005, page 36 >

Regulatory Impact

When do we include St. John’s Wort in the drug labeling?

Cytochrome P450 3A and P-gp substrates and where the products' effectiveness may be reduced upon co-administration of St. John's Wort

Labeling

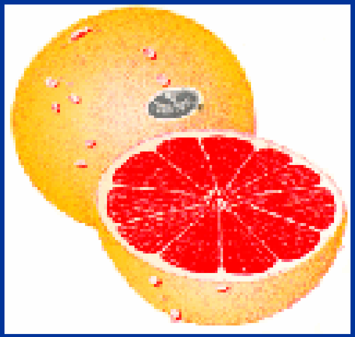
•Concomitant use of KALETRA and St. John's wort (hypericum perforatum)…...is not recommended.

Similar labeling for
- MIFEPREX (mifepristone)
- GLEEVEC (imatinib)
- $\geq$ 55 drug products and 2 St John’s wort products

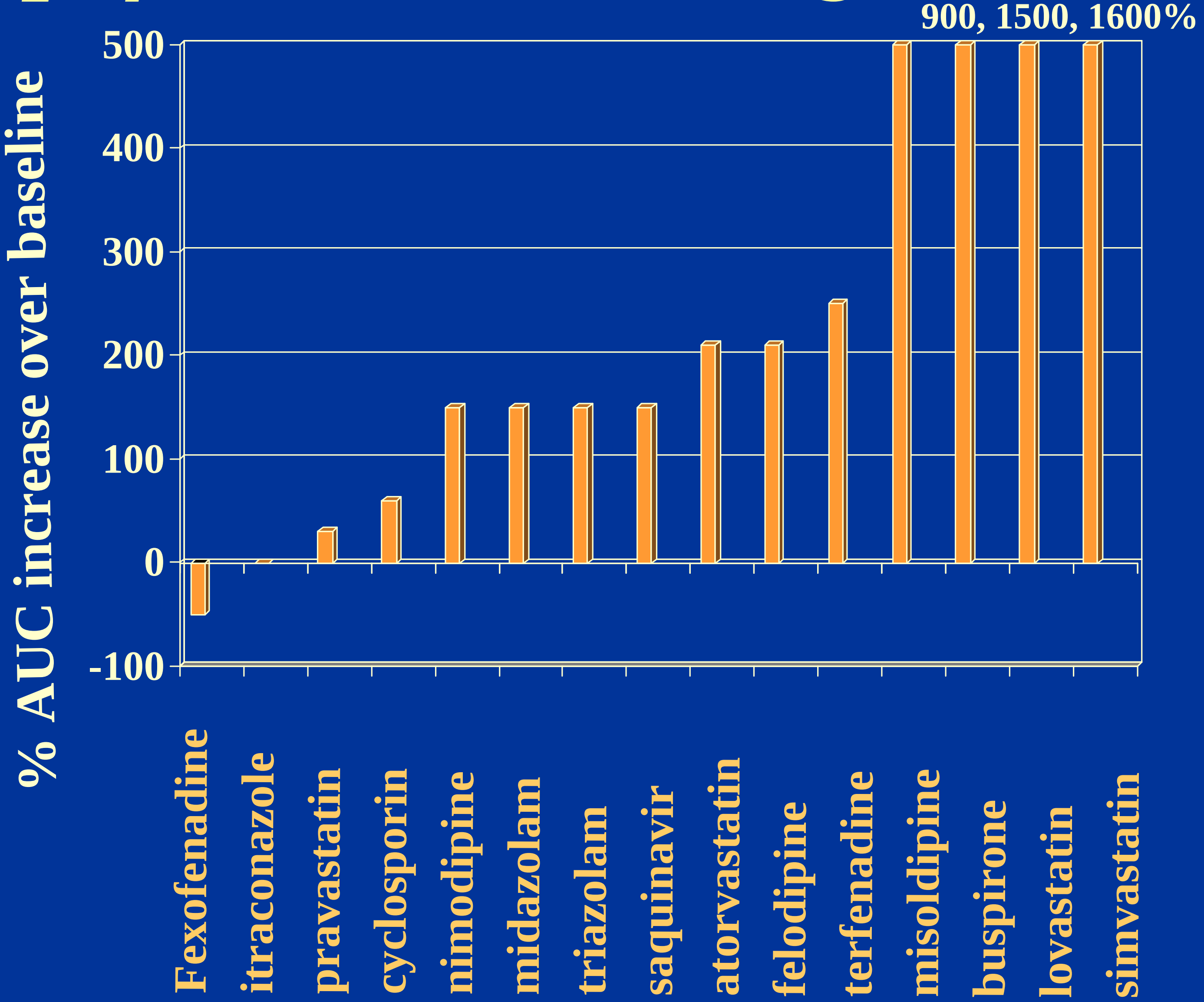
< http://www.fda.gov/cder/foi/label/2000
http://www.fda.gov/cder/foi/label/2000/20687lbl.htm
http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/57300800.htm>

Interactions with Citrus Fruit/Juices

Grape fruit juice



Grapefruit Juice - Drug Interactions



Case 1- lovastatin (1)

- 69 yo Caucasian male; started lovastatin concurrent with gemfibrozil, amlodipine, metoprolol, glyburide, trovafloxacin, vitamine E, metformin, aspirin, ciprofloxacin

- Early Oct 98, changed his usual orange juice to 8 oz grapefruit juice

- 13 Oct 98, diffuse muscle pain and high CPK

- ICU for rhabdomyolysis with acute renal failure, overlapping with chronic renal failure

<This case has been presented earlier by Park, Wei, Green, Chang at the FDA Science Forum, February 2000; Wei J et al at the AAPS annual meeting, November 1999>

Case 1- lovastatin (2)

- started IV fluid; d/c lovastatin and gemfibrozil gradually back on other medications
- CPK decreased (to 1,017 on 27 Oct 09); improved on muscle weakness
- Physician concluded drug interactions between grapefruit and lovastatin and gemfibrozil

=> told the patient to avoid grapefruit juice

Regulatory Impact

When do we include grapefruit juice in the drug labeling?

Cytochrome P450 3A substrates with low oral bioavailability

-labeling in ≥ 28 drug products

Dosage and Administration:
Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of *cyclosporine (Neoral)* , thus should be avoided

Warnings/Precautions:
To avoid possible serious side effects, avoid drinking large quantities of grapefruit juice (more than on quart daily) while on *simvastatin (ZOCOR)* (see ….Muscle)

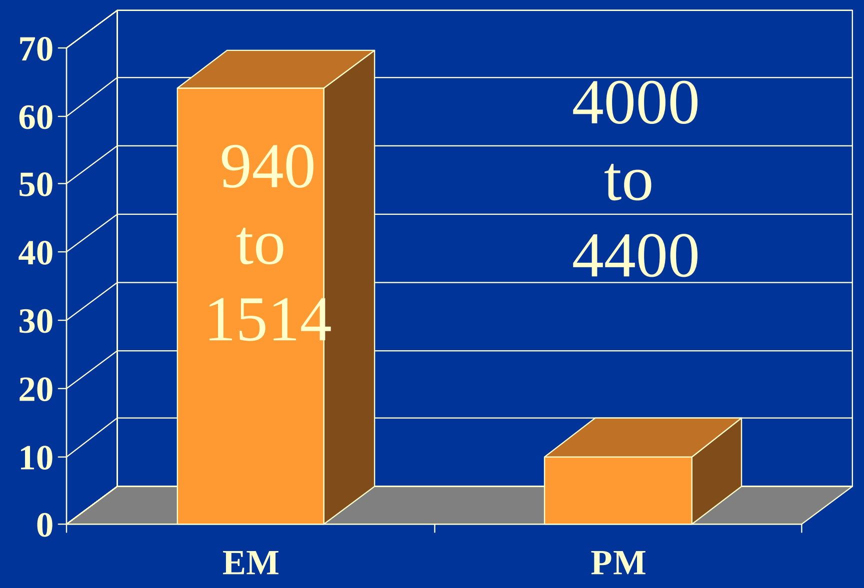
<http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/57301293.htm#PDRCON01, 11/99 update>

Pharmacogenetics

Drug Interactions: CYP2D6 substrates

Metoprolol

% AUC increase by diphenhydramine



Hamelin *et al*. Clin Pharmacol Ther 2000;67:466-77

Table 7. The effect of genotypes on the extent of drug interactions

Substrate (enzyme)	Inhibitor or inducer	Outcome (changes in plasma AUC or concentrations of substrates)	ref
Atomoxetine (CYP2D6)	fluoxetine, paroxetine	AUC increase 6-8 fold in EM; no change in PM expected	21
Metoprolol (CYP2D6)	diphenhydramine	Higher inhibition in EM vs. PM (fold vs. fold)	76
Tamoxifen (CYP2D6)	paroxetine	Greater reduction in plasma levels of endoxifen (active metabolite of tamoxifen formed via CYP2D6) in homozygous EM as compared to patients with at least one variant allele	77
Diazepam (CYP2C19)	omeprazole	No inhibition in PM	78
Omeprazole (CYP2C19)	fluvoxamine	AUC increased 3-6 fold in EM; no changes in PM	79
Omeprazole (CYP2C19)	Gingko Bloba	Higher induction in EM	80

< Huang, S-M, Lesko, LJ, "Application of Pharmacogenomics in Clinical Pharmacology" - in Part I: Molecular Medicine, Correlation between genes, diseases and biopharmaceuticals, in "Modern Biopharmaceuticals- Design, Development and Optimization", Ed., Jorg Knablein and RH Muller, Wiley, VCH (in press) >

Summary:

1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish "Therapeutic equivalence boundaries"
5. Labeling language needs to be useful and consistent
6. Need additional means in communicating risks

References

- Guidance for industry: In vivo metabolism/drug interactions: Study design, data analysis and recommendation for dosing and labeling (Issued 11/24/1999, Posted 11/24/1999); http://www.fda.gov/cder/guidance/index.htm; http://www.fda.gov/cder/guidance/2635fnl.pdf
- Tucker, Houston and Huang, Clin Pharm Ther August 2001; 70(2):103
- Bjornsson, Callaghan, Einolf, et al, J Clin Pharmacol, May 2003; 43(5):443
- Yuan, Madani, Wei, Reynolds, Huang, Drug Metab Disp, December 2002; 30(12) 1311
- Labeling guideline. Federal Register 65[247], 81082-81131. December 22, 2000.
- FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues and challenges in the evaluation and labeling of drug interaction potentials of NME Rockville, MD. April 23, 2003; http://www.fda.gov/ohrms/dockets/ac/03/slides/3947s2.htm; http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3947T2.htm
- FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm
- Huang, S-M, Lesko, L, J Clin Pharmacology, June 2004
- Huang, S-M, Hall, S, Watkins, P, et al, Clin Pharmacol Ther, Jan 2004
- FDA Food and Drug Administration Concept Paper: Premarketing Risk Assessment. March 3, 2003, http://www.fda.gov/cder/meeting/riskManageI.htm; http://www.fda.gov/cder/meeting/riskManageII.htm; http://www.fda.gov/cder/meeting/riskManageIII.htm
- Huang, S-M, Drug-drug interactions, in Applications of Pharmacokinetic Principles in Drug Development, Ed. Rajesh Krishina, Kluwer Academic/Plenum Publishers, 2003